UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,066	09/20/2001	Hazire Oya Alpar	41577/263691	4735

23370 7590 10/01/2004

JOHN S. PRATT, ESQ
KILPATRICK STOCKTON, LLP
1100 PEACHTREE STREET
ATLANTA, GA 30309

EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 10/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,066	ALPAR ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 11-23* is/are pending in the application.

4a) Of the above claim(s) *7-10 and 24-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 11-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I in the reply filed on October 6, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 7-10 and 24-35 are withdrawn from consideration. Claims 1-6 and 11-23 are under consideration in this office action.

Specification

3. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-6 and 11-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 1 is drawn to a polycationic carbohydrate or pharmaceutically acceptable derivative thereof wherein the polycationic carbohydrate comprises a water-soluble alkylated chitosan or a pharmaceutically acceptable salt or derivative thereof, a cationic polypeptide, cationic polyamino acid, quaternary ammonium compound or a mixture thereof for use as an immunostimulant. The written description in this case only sets forth immunostimulants such as chitin derivatives, chitosan or chemically modified forms of chitosan, therefore the written description is not commensurate in scope with the claims since they are drawn to a mixture thereof. Neither the specification nor the claims teach a mixture of cationic polypeptide, cationic polyamino acid, and/or quaternary ammonium compounds thereof. Neither the claims nor the specification teach how to obtain mixtures thereof. There is no guidance as to what mixtures can or cannot be used together in the composition being claimed. The specification does not include structural examples of mixtures thereof. Thus, the resulting mixture thereof could result in composition not taught and enabled by the specification.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

With the exception of specifically named chitin derivatives such as chitosan or chemically modified forms of chitosan, the skilled artisan cannot envision the detailed structure of the mixtures thereof, thus conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. An adequate description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. Furthermore, *In The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of by only their functional activity does not provide an adequate description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of compositions falling within the scope of the claimed genus. Therefore only the recited chitin derivatives such as chitosan or chemically modified forms of chitosan and not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

5. Claims 1-6 and 11-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is unclear. Claim 1 is drawn to a polycationic carbohydrate or pharmaceutically acceptable derivative thereof wherein the polycationic carbohydrate comprises a water-soluble alkylated chitosan or a pharmaceutically acceptable salt or derivative thereof, a cationic polypeptide, cationic

polyamino acid, quaternary ammonium compound or a mixture thereof for use as an immunostimulant. However it is unclear if the polycationic carbohydrate or pharmaceutically acceptable derivative thereof comprises 1) a water-soluble alkylated chitosan 2) a cationic polypeptide, 3) a cationic polyamino acid and 4) quaternary ammonium compound OR if the cationic polypeptide, cationic polyamino acid, quaternary ammonium compound or mixtures thereof are particular examples of a polycationic carbohydrate or pharmaceutically acceptable derivatives. Therefore clarification of the claim language is required to overcome the rejection.

6. It is also unclear how to define a pharmaceutically acceptable salt. The claim does not recite what is comprised within the pharmaceutically acceptable slat. Thus the metes and bounds of the claim are unclear and clarification is required to overcome the rejection.

7. Regarding claim 2, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

8. Dependant claims 2-6 and 11-23 refer to “a polycationic carbohydrate” or “a pharmaceutical composition”, however the suggested claim language is to use of the article “the.” Therefore the suggested claim language is “the polycationic carbohydrate” or “the pharmaceutical composition.”

9. The term "biologically active agent" in claims 4,6,16 and 23 is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Thus the metes and bounds of the claim are unclear and appropriate clarification is required to overcome the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-2, 4-6, 11-12, 16 and 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Illum (WO 97/20576).

The claims are drawn to a polycationic carbohydrate or pharmaceutically acceptable derivative thereof wherein the polycationic carbohydrate comprises a water-soluble alkylated chitosan or a pharmaceutically acceptable salt or derivative thereof, a cationic polypeptide, cationic polyamino acid, quaternary ammonium compound or a mixture thereof for use as an immunostimulant. The dependent claims are drawn to chitosan derivatives and pharmaceutical compositions comprising diluents, microparticles, and biologically active agents.

The claims are interpreted to define the polycationic carbohydrate or pharmaceutically acceptable derivative thereof to include cationic polyamino acid, quaternary ammonium compound, mixtures thereof, to be drawn to chitosan or other chemically modified forms of chitosan. See page 4 of the instant specification which provides this definition.

Illum teach vaccine compositions for intranasal administration wherein the compositions comprise one or more antigens, an effective adjuvant and chitosan. The invention further relates to methods of enhancing the immunogenicity of intranasally administered antigens and the use of antigens in combination with an adjuvant for the manufacture of a vaccine composition for intranasal administration to immunize a mammal against a specific disease (page 1 lines 1-6). Certain adjuvants have shown that when co-administered with vaccine antigens they further boost the effectiveness of the vaccine compositions by stimulating the immune response (page 2 lines 17-20). Chitosans are derivatives of chitin or poly-N-acetyl-D-glucosamine wherein the greater proportion of the N-acetyl groups have been removed (page 2 lines 25-28). Chitosans are known to be mucosal absorption enhancers and upon intransal co-administration, chitosan enhances the immune response of antigens and provide an enhanced effect upon the host (page 3 lines 1-6). The invention also teaches that vaccines are typically administered parenterally via injections (page 1 lines 20-21). Suitable antigens include tetanus antigens, such as the tetanus toxoid and diptheria antigens, such as the diphtheria toxoid (pages 4-5 lines 23-1). Preferably the chitosan is water-soluble and may be produced by deacetylation methods (page 5 lines 20-24). Particular chitosans

such as chitosan glutamate may be commercially purchased (page 5 lines 25-28). Thus, this is a polycationic carbohydrate which is a water-soluble alkylated chitosan just as instantly claimed. The intranasal compositions can be formulated in the form of microspheres (page 6 lines 22-24). Thus the composition comprises a formulation using microparticles or microspheres along with the chitosan and biologically active agents just as claimed. The compositions may include excipients which are typically included in compositions, examples of excipients include preservatives, viscosity agents, tonicity agents, buffering agents and the like (page 6 lines 25-29). Example 1 teaches the preparation of an influenzae surface antigen and chitosan glutamate composition made up in a phosphate buffered saline solution and further comprising the adjuvant alhydrogel. Example 1 teaches that the mice received intranasal or subcutaneous administration. The tables and figures show the levels of protection for the mice. Thus the pharmaceutical compositions of Illum comprising biologically active agents or antigens which are capable of generating a protective immune response in an animal along with the polycationic carbohydrate chitosan have been taught.

Therefore Illum teach a polycationic carbohydrate or pharmaceutically acceptable derivative wherein the polycationic carbohydrate comprises a water-soluble alkylated chitosan or a pharmaceutically acceptable salt or derivative thereof for use as an immunostimulant which is intranasally or parenterallly administered. Illum also teach compositions comprising chitosan derivatives and pharmaceutical compositions comprising diluents, microparticles, and biologically active agents such as bacterial antigens.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 13-15,17 and 20-22 rejected under 35 U.S.C. 103(a) as being unpatentable over Illum in view of Eyles et al. Illum has been discussed above, however Illum does not discuss a composition comprising the combination of the V and F1 antigen of *Yersinia pestis* and compositions which comprise cationic pluronics or nanospheres.

The claims are drawn to claims comprising a combination of the V and F1 antigen of *Yersinia pestis* and compositions which comprise cationic pluronics or nanospheres.

Eyles et al., teach intra-nasal administration of poly-lactic acid microspheres co-encapsulated with *Yersinia pestis* subunits that confer protection from pneumonic plague in mice. *Yersinia pestis* has a capsule that surrounds the bacterium and contain a protein-polysaccharide complex, which was termed the F1 subunit (page 698). The F1 antigen confers resistance to phagocytosis (page 698). Similarly, the secreted V antigen exerts local anti-inflammatory effects via modulation of tissue cytokine levels (page 698). Both F1 and V antigens are protective, although there is an additive effect

in the combination (page 698). Encapsulation of antigenic material within microparticulate polymeric carriers, such as poly-DL-lactide (PLA) microspheres serves to protect the labile vaccines from degradation and enhance adsorption (page 699). The commercially purchased poly-(L-lactide) has a molecular weight of 100 kDa and used in a modified double emulsion solvent evaporation method (page 699). Microencapsulation of the subunits comprised both the V and F1 antigen wherein the microspheres were later lyophilized (page 699). Eyles et al., also teach that the intra-nasal route is an attractive route for mucosal delivery (page 699).

It is noted that the instant specification defines microparticles, microspheres and nanospheres as equivalent terms which are cationic pluronic compounds. Therefore the cationic pluronic compounds make up these particles and spheres. Thus Eyles et al., teach the use of such microparticles and/or spheres and the associated chemical compounds and the claimed ratios. It is noted that no more than routine skill is required to change the concentration or ratio of well known compositions and such changes do not impart patentability.

Therefore, it would have been prima facie obvious at the time of applicants' invention to have used the known polycationic carboyhdrates and pharmaceutical compositons as taught by Illum and modify the compositions to include the combination of the V and F1 antigen of *Yersinia pestis* comprised within nanospheres as taught by Eyles et al., because Eyles et al., teach that it is well known in the art to make and use phamaceutical compostions that protect labile vaccines from degradation and enhance adsorption. One would have a reasonable expectation of success since no more than

routine skill would have been required to use commerically available microspheres containing the antigen combination when the art teaches the success and usefulness of using both the protective F1 and V antigens. Moreover, no more than routine skill would have been required to the modify the well known composition since the modification merely incorporates using equivalent antigenic products and well known microsphere encapsulation for the well known purpose of enhancing mucosal adsorption and inducing immunity in a subject.

12. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Illum in view of Kotze et al. Illum has been discussed above, however Illum does not discuss a composition comprising trimethylchitosan. The claim is drawn to a polycationic carbohydrate that is a trimetylchitosan.

Kotze et al., teach N-trimethyl chitosan chloride as a potential absorption enhancer across mucosal surfaces. Chitosan is a polycationic polymer with numerous applications (page 1197). Chitosan is highly available at low cost, highly biocompatible, biodegradable and easily chemically modified (page 1197). Chitosan has gel-forming properties and can be used as a drug carrier in hydrocolloids (page 1197). Chitosan is also used as a constituent in polymeric matrix systems, microspheres and microcapsules for sustained release of water-soluble drugs (page 1197). The mucoadhesive properties of chitosan and its ability to act as an absorption enhancer has led to its use as a coating material for multilamellar liposomes (page 1197). Thus the water-soluble chitosan derivative N-trimethyl chitosan chloride effects the

permeability of cells and increases the transport of large hydrophilic compounds such as peptide drugs (page 1197).

Therefore, it would have been prima facie obvious at the time of applicants' invention to have used the known polycationic carboyhdrates as taught by Illum and modify the compositions to include the N-trimethyl chitosan as taught by Kotze et al. Kotze et al., teach that it is well known in the art to make and use polycationic carbohydrates that are highly available at low cost, highly biocompatible, biodegradable and easily chemically modifiable. One would have a reasonable expectation of success since no more than routine skill would have been required to use chitosan as a constituent in the polymeric matrix systems, wherein the systems include nanospheres which are known to achieve the sustained release of water-soluble drugs. Moreover, no more than routine skill would have been required to modify the well known composition since the modification merely incorporates using the mucoadhesive properties of chitosan and its ability to act as an absorption enhancer.

13. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Illum and Eyles et al., and further in view of Kotze et al. Illum and Eyles et al., have been discussed above, however neither discuss a composition comprising cationic pluronic which are surface modified with chitosan.

Kotze et al., have been discussed above for teaching that the mucoadhesive properties of chitosan (page 1197). Chitosan is also known for its ability to act as an

absorption enhancer which has led to chitosan's use as a coating material for multilamellar liposomes (page 1197).

Therefore, it would have been prima facie obvious at the time of applicants' invention to have used the known pharmaceutical compostions as taught by Illum and Eyles et al., to include nanospheres or cationnic pluronic compounds which are surface modified with chitosan as taught by Kotze et al. One would have a reasonable expectation of success since no more than routine skill would have been required to use chitosan as the coating material for multilamellar liposomes since the prior art already teaches its beneficial use. Moreover, no more than routine skill would have been required to the modify the well known composition since the modification merely incorporates using the mucoadhesive properties of chitosan and its ability to act as an absorption enhancer.

14. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable by Illum (WO 97/20576) in view of Eyles et al. The claims is drawn to a method for producing a pharmaceutical composition wherein the method comprises encapsulating a biologically active agent in a material in the presence of a polycationic carbohydrate.

Both Illum and Eyles et al., have been discussed above. Illum further teaches that the invention further relates to methods for using antigens in combination with an adjuvant for the manufacture of the vaccine composition for intranasal administration to immunize a mammal against a specific disease (page 1 lines 1-6). Eyles et al., teach the encapsulation of the antigens.

Therefore, it would have been prima facie obvious at the time of applicants invention to have used the known method of producing pharmaceutical compostions as taught by Illum to include encapsulation of the bacterial antigens as taught by Eyles et al. One would have a reasonable expectation of success since no more than routine skill would have been required to use a combination of protective antigens comprised within polycationic carbohydrates. Moreover, no more than routine skill would have been required to the modify the well known composition since the modification merely incorporates using encapsulation of antigenic material within microparticulate polymeric carriers to protect labile vaccines from degradation and enhance adsorption.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
September 21, 2004

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600